Acetaminophen toxicosis in a Dalmatian

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Abstract — An 11-year-old, spayed female Dalmatian was presented with suspected acetaminophen toxicosis. The dog was severely depressed. Methemoglobinemia, facial edema, and hemoglobinuria responded to treatment with intravenous fluids, N-acetylcysteine, ascorbic acid, and sodium bicarbonate. There was no clinical evidence of hepatic damage typical of acetaminophen toxicity in the dog.

Résumé — Toxicose à l'acétaminophène chez un Dalmatien. Un Dalmatien femelle de 11 ans, stérilisé, a été présenté pour une toxicose présumée à l'acétaminophène. Le chien était fortement déprimé. La méthémoglobinémie, l'œdème facial et l'hémoglobinurie ont répondu au traitement aux fluides intraveineux, à la N-acétyl-cystéine, à l'acide ascorbique et au bicarbonate de soude. Il n'y avait pas d'indices cliniques d'atteintes hépatiques typiques des effets toxiques de l'acétaminophène chez le chien.

(Traduit par Docteur André Blouin)

Can Vet J 2003;44:142–144

An 11-year-old, 25-kg, spayed female Dalmatian was suspected of consuming an unknown number of 500-mg acetaminophen tablets (Extra-strength Tylenol; McNeil Consumer Healthcare, Fort Washington, Pennsylvania, USA). The owner discovered the dog beside an empty bottle of tablets, 3 to 4 h prior to presentation. The owner reported no previous medical problems.

Initial physical examination revealed marked depression, lethargy, and mild dehydration (< 5%); markedly cyanotic mucous membranes, a grey-blue tongue, and a capillary refill time (CRT) were within normal limits (< 2 s). The dog exhibited whole body tremors, salivated excessively, and was tachycardic (180 beats/min), tachypnic (42 breaths/min), and normothermic (37.9°C). A small volume of red-brown urine was voided during the examination.

A cephalic catheter was placed and 0.9% sodium chloride solution was administered at a rate of 6 mL/kg bodyweight (BW)/h. Blood was collected prior to initiating fluid therapy for a complete blood cell (CBC) count and biochemical profile. On the basis of history and findings on physical examination, a definitive diagnosis of acetaminophen toxicosis was made.

Gastric lavage and emesis with activated charcoal were not pursued because of the time frame in which the dog had initially ingested the tablets. The antidote, N-acetylcysteine, was not available in the clinic pharmacy and an order was placed at a local hospital for humans. In the meantime, therapy was initiated by administering 8.4% sodium bicarbonate solution (Amvet, Yaphank, New York, USA), 50 mg/kg BW, PO, and ascorbic acid (Phoenix Pharmaceutical, Phoenix, Arizona, USA), 30 mg/kg BW, SC. Approximately 1 h after this therapy had been initiated, a 20% solution of N-acetylcysteine (Mucosil; DEY, Napa, California, USA) was obtained and the first dose, 140 mg/kg BW, was administered slowly, IV, in an equal volume of saline. Therapy was continued with N-acetylcysteine at 70 mg/kg BW, diluted in an equal volume of isotonic saline, q6h for 8 additional treatments. Ascorbic acid was continued at 30 mg/kg BW, SC, q6h for 7 treatments and sodium bicarbonate at 50 mg/kg BW, PO, ql2h for 5 treatments. Intravenous fluid therapy with 0.9% sodium chloride was slowed to a rate of 2.4 mL/kg BW/h after hydration status was normal (within the first hour of presentation) and was continued until the dog was discharged from the clinic on day 4.

The blood collected prior to initiating therapy on day 1 was moderately brown in color, indicating methemoglobinemia. The CBC count revealed only a mild stress leukogram. The hematocrit and erythrocyte count were within normal limits. Mild poikilocytosis and anisocytosis, but no heinz bodies, were observed on a blood smear. The biochemical profile revealed elevated glucose (9.09 mmol/L; reference range, 3.86 to 6.6 1 mmol/L) and low phosphorous (0.29 mmol/L; reference range, 0.55 to 1.45 mmol/L). All other analytes, including the liver enzymes alanine aminotransferase (ALT) and alkaline phosphatase (ALP), were well within normal reference intervals.

Six hours after initial therapy, the dog was inappetant and lethargic but less depressed, had pink mucous membranes and a CRT < 2 s, and was well hydrated. Although tachycardia persisted, respiratory rate and rectal temperature were normal. The dog's face was swollen, particularly the periorbital region, with edematous conjunctiva and bilateral protruding nictitans. At this time, a second biochemical profile revealed hypoproteinemia

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(50 g/L; reference range, 55 to 76 g/L) and mild hypoalbuminemia (24 g/L; reference range, 25 to 36 g/L), consistent with ongoing fluid therapy. Urinalysis of a clear voided sample revealed a specific gravity of 1.018 and mild ketonuria, reflective of the diuretic effect of fluid therapy and fasting, respectively. Urine color appeared normal.

On day 3, the dog's appetite remained poor and marked facial edema was still present; however, the dog was far less depressed and lethargic. Heart rate, respiratory rate, and rectal temperature were normal and mucous membranes remained pink. On day 4, a CBC count and biochemical profile were again repeated. The CBC count revealed a mild regenerative anemia (hematocrit 30 L/L; reference range, 37 to 55 L/L). All biochemical analytes were within normal limits. Facial edema had decreased and appetite had improved. The dog was discharged on day 4, showing no apparent liver toxicity or persistent methemoglobinemia. The owner was encouraged to monitor appetite, energy levels, and mucous membrane color in case the anemia worsened.

In dogs, clinical signs of acetaminophen toxicity are generally seen with doses in excess of 200 mg/kg BW (1); whereas, cats are much more sensitive, exhibiting signs of toxicity at doses of approximately 60 mg/kg BW (2). In this case, because of the severe clinical signs, it was presumed that the dose had exceeded 200 mg/kg BW, which would have been accomplished with consumption of a minimum of 10, 500-mg tablets of acetaminophen. What was unusual was that this dog primarily displayed signs of blood toxicity, which is more commonly demonstrated in cats.

In dogs, the liver is typically the primary target of damage; however, no clinical evidence of hepatic damage (abdominal pain, vomiting, or icterus with elevated levels of ALT, ALP, and total bililrubin) was observed in this dog. Dogs exhibit the early effects of acetaminophen toxicosis within 4 to 12 h: progressive cyanosis, tachypnea, and dyspnea, depending on the degree of methemoglobinemia. Signs attributable to hepatic necrosis usually occur approximately 36 h after the ingestion of acetaminophen, that is, after sufficient time for significant damage to have occurred (1). It is atypical for methemoglobinemia to occur in dogs without subsequent clinical evidence of hepatic damage. In this case, however, acute toxicity was treated soon after exposure, which may explain, in part, the lack of involvement of the liver.

Acetaminophen undergoes both toxic and nontoxic biotransformation in the liver (4). In dogs, most of a dose of acetaminophen is conjugated with glucuronide and sulfate by transferase enzymes, which are deficient in the cat (2–4). In the dog, only a small portion of a dose is converted to reactive metabolites by the cytochrome P-450-dependent mixed function oxidase (MFO) system (2–4). The reactive metabolites formed may subsequently become conjugated with glutathione (GSH) and excreted in the urine as nontoxic metabolites (2,3). The cytotoxic metabolite, N-acetybenzoquinoneimine, may bind liver proteins and cause centrilobular necrosis (4). Likewise, a free radical may form through the MFO system and cause oxidative damage to cellular molecules, such as hemoglobin, forming methemoglobin (3,4). Cimetidine, a potent MFO inhibitor in the liver, has been used in cats to reduce toxic metabolite production and might have been beneficial in this case. Hepatic damage may occur when glucuronide and sulfate conjugation pathways are saturated and GSH is depleted by excess acetaminophen metabolites. When this occurs, the reactive metabolites produced by the biotransformation of acetaminophen in the MFO system are free to bind to hepatic macromolecules and inflict oxidative damage (2,3). Generally, this damage does not occur until GSH levels have reached about 20% of normal (2,3). The antidote, N-acetylcysteine, works primarily to restore the levels of GSH by hydrolysis to cysteine, which is a substrate in GSH synthesis. It also provides sulfhydryl groups for the reactive metabolites to bind to, for excretion in the urine (3). One study in mice documented a significant difference with age and the degree of acetaminophen-induced hepatotoxicity (4). In young mice, there was a protective effect on the liver attributed to an immature MFO system and a more rapid rate of GSH resynthesis. In adult mice, varying degrees of hepatotoxicity were attributed to differences in which hepatic proteins were covalently bound by reactive metabolites. These researchers concluded that the critical determinant of hepatotoxicity might be the specific proteins that are targeted, rather than the total amount of protein binding. The liver has a tremendous reserve capacity, and perhaps the degree of protein binding experienced by the dog in this case was not sufficient to cause clinically evident hepatic damage. However, it may also be possible that specific protein susceptibility to metabolite binding varies among dogs.

The degree of hepatocyte damage and methemoglobin formation is also influenced by preexisting levels of GSH, selenium, and glutathione peroxidase. Selenium is an important component of the enzyme glutathione peroxidase, which is necessary to protect the cell from oxidative damage (3). In a study in which rats were fed selenium-deficient diets, lower activities of glutathione reductase and glutathione peroxidase enzymes were observed (5). Additionally, in another study, rats that were treated with selenium prior to administration of toxic doses of acetaminophen were protected against hepatotoxicity compared with untreated control rats (6). The glutathione conjugating system was enhanced, as were the activities of the enzymes responsible for synthesis of GSH and catalyzation of conjugation reactions between GSH and the reactive metabolites. The major protective effect, however, was thought to be due to an increased amount of glucuronide conjugation in selenium-fed rats. This enhanced conjugation effectively reduced the amount of acetaminophen that was delivered to the MFO system to be converted into toxic metabolites. It is possible, in the case presented here, that there was a minor degree of selenium deficiency that allowed more MFO metabolism of acetaminophen, thus producing more free radical available to oxidize hemoglobin to methemoglobin.

It may also be speculated that a genetic predisposition, similar to that in cats, may have existed in this dog, in that a deficiency of nontoxic conjugation pathways might have been responsible for shifting acetaminophen biotransformation into the MFO system toward free radical production. Alternatively, similar to humans, that there is an inherited, congenital condition that

involves a deficiency in methemoglobin reductase, the enzyme responsible, together with NADH, for the conversion of methemoglobin to hemoglobin (3,7). Although these conditions were not identified in the dog presented here, it is important to consider them as possibilities.

This case demonstrated the variation in clinical presentation that might occur in dogs after ingesting large doses of acetaminophen and the possible effect of early and aggressive treatment. Other atypical cases have been reported, in which dogs displayed abnormal blood parameters including methemoglobinemia and heinz bodies with only minimal hepatic damage (8,9). These variations may be due to a multitude of interrelated physiological factors and therapies. It is important to initiate antidotal therapy early in acute acetaminophen toxicosis to achieve the greatest chances for a successful and favorable recovery prognosis.

Acknowledgments

The author thanks the staff at the Quakertown Veterinary Clinic, and Drs. Boermans and Butler of the Ontario Veterinary College for their assistance. CVJ

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BOOK REVIEW

COMPTE RENDU DE LIVRE

Budras K-D, Sack WO, Röck S. ***Anatomy of the Horse: An Illustrated Text, 3rd ed.*** Iowa State University Press, Ames, Iowa, 2001, 152 pp, 3-87706-620-8, US$74.95.

The Anatomy of the Horse: An Illustrated Text is the 2nd volume in a series of 3 that will describe the anatomy of major domestic mammals. The authors' aim is to succinctly illustrate the clinically relevant details of equine anatomy. The book has been designed for veterinary students and equine practitioners, but it should also serve veterinary anatomists and surgeons.

This edition is somewhat longer (152 pages) than the previous edition, but it maintains the same structure. It is divided into 3 parts. In the first part, 80 pages of opposing text and color plates, the anatomy of various regions is described, using a topographic approach. The second part comprises 20 pages of tables that summarize details such as attachment, nerve supply, and function of muscles; position and field of drainage of lymph nodes; and the origins and distribution of peripheral nerves. This information is keyed to the color plates of part one. The last 25 pages deal with clinical problems involving the structures described in the first sections.

The topographical anatomy section is divided into the following regions: thoracic limb; pelvic limb; head; central nervous system; axial skeleton and neck; thoracic cavity; abdominal wall and cavity; and pelvis, inguinal region and urogenital organs. The hoof is described in minute detail with illustrations that aid one in comprehending its complex organization. Synovial structures (joints, bursa, and sheaths) of both the thoracic and pelvic limbs are clearly illustrated, their topographic limits are also mentioned in the text. This information, often limited in anatomy texts, is clinically pertinent to the practitioner, since traumatic or septic involvement of these structures will have an important impact on prognosis. A criticism I have is that the color plates are annotated with numbers referring to the same structures depicted on other plates; these can lead to confusion as the reader is forced to change pages frequently to obtain complete information about the structures under investigation.

Information in the second part is presented in tabular form, allowing numerous details to be concisely listed; the section on cranial nerves is especially thorough. This second part will allow rapid consultation by the busy student and veterinarian alike.

The authors are to be commended for addressing clinical problems relating to structures described in the first 2 parts of the book. Too often, the importance of anatomy to veterinary practice is overlooked in classical anatomy texts. This third section will encourage veterinary students to apply their newfound anatomic knowledge to clinical situations where medical imagery and surgery predominate, and thus helping them to retain pertinent information.

Previous editions of this book have become classical reference texts as a result of the quantity and quality of their illustrations. Although the detail of the latter is occasionally overwhelming, the text summarizes and facilitates comprehension. This 3rd edition should aid horse owners and veterinary students, practitioners and surgeons, as well as academic anatomists to obtain knowledge of equine structures in a convenient way.

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